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(71) Applicant: **VIRGINIA COMMONWEALTH UNIVERSITY** [US/US]; 1101 East Marshall Street, Richmond, VA 23298 (US).

(72) Inventor: **FARRELL, Nicholas**; 102 North Stafford Avenue, Richmond, VA 23220 (US).

(74) Agents: **WHITHAM, Michael, E.** et al.; McGuireWoods, LLP, Suite 1800, 1750 Tysons Blvd, McLean, VA 22102 (US).

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(54) Title: TRANSPLATINUM COMPLEXES AS CYTOTOXIC AND ANTICANCER AGENTS

(57) Abstract: The invention provides a method for enhancing the water solubility of cytotoxic *trans*-platinum complexes. The present invention also provides a method for killing tumor cells, and a method for the treatment of tumors by the administration of a cytotoxic platinum coordination complex of the general formula *SP*-4-2[PtX(L)(L')(B)]$^+$.

TRANSPLATINUM COMPLEXES AS CYTOTOXIC AND ANTICANCER AGENTS

This invention was made using funds from grants from the National Science Foundation having grant number 5-23175. The government may have certain rights in this invention.

DESCRIPTION

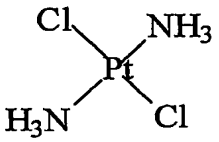
BACKGROUND OF THE INVENTION

Field of the Invention

The invention generally relates to a method for water-solubilization of cytotoxic *trans*-platinum compounds and to a method of killing tumor cells. In particular, the invention provides cytotoxic platinum compounds of the general formula *SP*-4-2-$[PtX(L)(L')(B)]^+$ for the treatment of tumors.

Background of the Invention

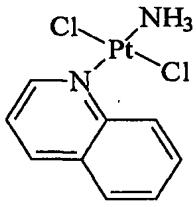
The use of cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, and carboplatin, $[Pt(CBDCA)(NH_3)_2]$ (CBDCA=1,1-cyclobutanedicarboxylate), in the treatment of certain cancers is well-established. Nevertheless, there is a continued interest in the design of structurally novel platinum compounds that show antitumor activity complementary to that of the clinical drugs. The fact that transplatin, *trans*-$[PtCl_2(NH_3)_2]$,



transplatin

was found to be therapeutically inactive, has been considered a paradigm for the structure-activity relationships (SAR) of platinum(II) antitumor compounds; *trans*-Pt compounds have been dismissed as ineffective *in vivo* agents.

However, the presence of a planar ligand such as pyridine or quinoline, e.g., in *trans*-$[PtCl_2(NH_3)(quinoline)]$,



trans-$[PtCl_2(NH_3)(quinoline)]$

dramatically enhances the in vitro cytotoxicity of the *trans* geometry [Farrell, N., Kelland, L.R., Roberts, J.D. and Van Beusichem, M.:Activation of the Trans Geometry in Platinum Antitumor Complexes. A Survey of the Cytotoxicity of Trans Complexes Containing Planar Ligands in Murine L1210 and Human Tumor Panels and Studies on Their Mechanism of Action. Cancer Res. 52:5065 (1992); Van Beusichem, M. and Farrell, N.: Activation of the Trans Geometry in Platinum Antitumor Complexes. Synthesis, Characterisation and Biological Activity of Complexes with Planar Ligands Pyridine, N-Methylimidazole, Thiazole and Quinoline. The Crystal and Molecular Structure of trans-dichlorobis(thiazole)platinum(II). *Inorg. Chem.* 31:634 (1992)] The cytotoxic activity of such "nonclassical" *trans*-platinum complexes has been discussed in terms of both an overall altered affinity toward biologically relevant (N and S) nucleophiles and unique DNA binding

modes. Importantly, the newer *trans*-platinum compounds containing planar ligands display a different profile of cytotoxicity in comparison to cisplatin and retain their cytotoxic activity in cisplatin-resistant tumor cells. Thus, there is reason to believe that a *trans*-platinum compound in the clinic would have activity complementary to cisplatin, resulting in significant benefits to patients. However, such "nonclassical" *trans*-platinum species have been found to have limited bioavailability and, consequently, low *in vivo* activity. One possible explanation is lack of water solubility.

It would be highly desirable to have available additional platinum species for the treatment of cancer. It would be especially desirable if such compounds displayed high levels of cytotoxicity and were also water-soluble, thereby enhancing their bioavailability and potential *in vivo* usefulness for the treatment of tumors.

SUMMARY OF THE INVENTION

It is an object of this invention to provide a method for enhancing water-solubility and cytotoxicity of the *trans*-platinum geometry through production of cationic compounds.

It is a further object of this invention to provide a method for killing tumor cells and treating tumors in patients, comprising the step of administering to a patient in need thereof an effective amount of a platinum coordination compound of the general formula *SP*-4-2-$[PtX(L)(L')(B)]^+$ where X is an anionic ligand; L and L' represent ammines (NH_3) or substituted or unsubstituted heterocyclic amines where the substituents are electrophilic or nucleophilic, and L and L' may be the same or different, and B is a sulfoxide, usually dimethylsulfoxide R^2R^3SO (where R^2 = methyl and R^3 = methyl; however it should be understood that other alkyl substituted sulfoxides may be used in this invention and that R^2 and R^3 may be the same or different) or a heterocyclic nucleobase with a nitrogen in a ring which is connected to Pt.

In preferred embodiments of the present invention, the platinum coordination compound is *trans*-$[PtCl(Me_2SO)(pyridine)_2]^+$, or *trans*-$[PtCl(9\text{-ethylguanine})(NH_3)_2]^+$, or *SP*-4-2-$[PtCl(9\text{-ethylguanine})(NH_3)(thiazole)]^+$, or *SP*-4-2-$[PtCl(9\text{-ethylguanine})(NH_3)(benzothiazole)]^+$, or *SP*-4-2-[PtCl 9-ethylguanine)$(NH_3)(quinoline)]^+$, or *SP*-4-2-$[PtCl(9\text{-ethylguanine})(NH_3)(isoquinoline)]^+$, or *trans*-[PtCl(9-ethylguanine)

(4-picoline)$_2$]$^+$, or *trans*-[PtCl(1-methylcytosine)(NH$_3$)$_2$]$^+$, or *SP*-4-2-[PtCl (1-methylcytosine)(NH$_3$)(thiazole$_1$],$^+$ or *SP*-4-2-[PtCl(1-methylcytosine)(NH$_3$)(quinoline)]$^+$, or *SP*-4-2-[PtCl(1-methylcytosine)(NH$_3$)(*iso*quinoline)]$^+$. Administration may be oral or parenteral.

It is a further object of the instant invention to provide new compositions of matter in the form of platinum coordination compounds: *trans*-[PtCl(Me$_2$SO)(pyridine)$_2$]$^+$, *SP*-4-2-[PtCl(9-ethylguanine)(NH$_3$)(thiazole)]$^+$, *SP*-4-2-[PtCl(9-ethylguanine)(NH$_3$) (benzothiazole)]$^+$, *SP*-4-2-[PtCl(9-ethylguanine)(NH$_3$)(*iso*quinoline)]$^+$, *trans*-[PtCl (9-ethylguanine)(4-picoline)$_2$]$^+$, *trans*-[PtCl(1-methylcytosine)(NH$_3$)$_2$]$^+$, *SP*-4-2-[PtCl(1-methylcytosine)(NH$_3$)(thiazole)],$^+$ *SP*-4-2-[PtCl (1-methylcytosine)(NH$_3$) (quinoline)]$^+$, and *SP*-4-2-[PtCl(1-methylcytosine)(NH$_3$)(*iso*quinoline)]$^+$.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

Platinum compounds of the general formula [PtXA$_m$B$_{3-m}$], which show excellent solubility, have been previously described as anti-viral agents (United States Patent Application 09/095,565, the complete contents of which is herein incorporated by reference). Surprisingly, some of these compounds also display cytotoxic properties. Therefore, the present invention provides novel forms of such compounds, a method for water-solubilization of cytotoxic *trans*-platinum compounds, a method for the use of such compounds as cytotoxic agents, and a method of use of such compounds to treat tumors. These compounds are described by the formula *SP*-4-2[PtX(L)(L')(B)]$^+$.

It is an object of the present invention to provide a method of killing tumor cells and treating tumors by the administration of platinum complexes of the general formula:

SP-4-2[PtX(L)(L')(B)]$^+$

In this formula:

a) X represents an anionic ligand such as halogens (e.g., Cl, Br, or I), alkoxides (e.g., OR where R=CH$_3$, C$_2$H$_5$, or other lower alkyls), sulfhydryls (SR where R= CH$_3$, C$_2$H$_5$, or

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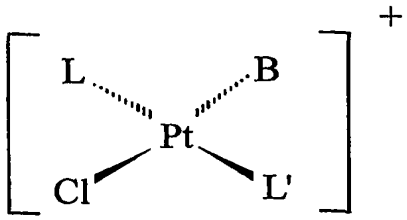
other lower alkyls, where C_{1-12} is preferred), and carboxylates ($RCOO^-$ where R=CH_3, C_2H_5, etc.).Chloride is the preferred anionic ligand;

b) L and L' represent ammines (NH_3 linked directly to the platinum metal), or substituted or unsubstituted heterocyclic amines, where the substituents are electrophilic or nucleophilic (e.g. C_{1-12} alkyl, $-NO_2$, -X (Cl, Br, I), $-NR_2$ where R is C_{1-12} alkyl, -COOR where R is C_{1-12} alkyl). Preferred heterocycles include but are not limited to thiazole, benzothiazole, imidazole, quinoline, isoquinoline, and picoline. Other useful heterocycles may include oxazole, indole, and acridine. L and L' may be the same of different. Further, L and L' are located "trans" to one another in the compounds. Note that, because four different substituents are present, "cis-trans" designations technically do not apply. The nomenclature "*SP*-4-2" follows the rules from Nomenclature of Inorganic Chemistry, Recommendations 1990, Blackwell Publicaitons, 1990. Edited by G.J. Leigh. [ISBN 0-632-02319-8; 0-6323-02494-1]. This nomenclature indicates that the compounds are square planar Pt II compounds in which the two centrally named substituents, L and L', are located *trans* to each other as depicted below:



c) B represents either of (i) or (ii):

i) a sulfoxide, R^2R^3 SO where R^2 and R^3 may be the same or different and represent alkyl or aryl substituents. In a preferred embodiment of the present invention, the sulfoxide is dimethylsulfoxide (where R^2 = methyl and R^3 = methyl). In yet another embodiment, R^2 = methyl and R^3 = benzyl;

ii) a nitrogen-containing nucleobase where the nitrogen is connected to the Pt moiety. Examples of such nucleobases include but are not limited to: purines and purine compounds (e.g. guanine, 9-ethylguanosine, adenine, hypoxanthine, xanthine, uric acid, caffeine, threobromine, and the like); pyrimidines and pyrimidine compounds (e.g. uracil, thymine,

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cytosine, methylcytosine, and the like); nucleosides (e.g. guanosine and the like); nucleotides (e.g. 5'-guanosinemonophosphate and the like); and oligonucleotides or defined polynucleotide sequences [e.g. deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or peptidonucleice acids (PNA)]. The preferred binding site of endocyclic nitrogens is N7 for purines and N3 for pyrimidines. Other ligands similar to nucleobases may also be used, for example, hydantoin.

The compounds in the present invention are usually cations and are prepared as salts. In depictions of the formulas in the text of the application, the counterion is omitted for simplicity. In preferred embodiments of the instant invention, the platinum compounds are prepared as nitrate salts. Other common counter-anions which may be utilized in the practice of the present invention include but are not limited to Cl^-, ClO_4^-, PF_6^-, and BF_4^-.

Chemical Syntheses

Nucleobase Compounds: *SP*-4-2-[PtCl(nucleobase)(L)(L')]NO_3. These compounds were prepared according to the published method (Bierbach U, Farrell N **(1998)** *JBIC* 3: 570-580). To a solution of :

i) 1 mmol of *trans*-[$PtCl_2$(L)(L')] (wherein L = L' = NH_3, or L = L' = pyridine), or

ii) *trans*-[$PtCl_2(NH_3)$(L)] where L = pyridine or a planar amine as above;

in 25 ml of anhydrous dimethylformamide (DMF) was added 0.170 g (1 mmol) of $AgNO_3$. After stirring this mixture at room temperature in the dark for 48 hours, the precipitated AgCl was filtered off through a Celite pad. To the filtrate was added (1 mmol) of 9-ethylguanine (or other suitable nucleobase) and the mixture was allowed to stir for 48 hours. The DMF was removed under reduced pressure at 30 °C. After addition of 50 mL of diethyl ether, the remaining oil solidified. The obtained crude products was recrystallized from methanol or cold water. Identity of products was confirmed by NMR spectroscopy and elemental analysis.

Sulfoxides: *SP*-4-2-[PtCl(R^2R^3 SO)(L)(L')]NO_3. These compounds contain a sulfoxide as ligand B. They were prepared in basically the same manner with slight modifications in work-up and crystallisation. The preparation is exemplified for the Me_2SO case.

***trans*-[PtCl(Me_2SO)($py)_2$]NO_3** To a suspension of *trans*-[$PtCl_2(py)_2$] (1.0 g, 2.4 mmol) in 30 mL of MeOH was added $AgNO_3$ (0.4 g, 2.4 mmol) and Me_2SO (2 mL, 2.2 g,

28 mmol). The reaction mixture was stirred at 80 °C overnight. The insoluble AgCl precipitate was filtered off and the filtrate was evaporated down. To the oil was added 2 ml of MeOH when a white solid precipitated out after stirring for about 10 minutes. Ether was then added to intensify the precipitation. After cooling overnight, the white solid was filtered off and recrystallized from hot MeOH/ether. The product was dried in vacuum with heat. Yield 66 %. Anal. Calcd. for $C_{12}H_{16}ClN_3O_4SPt$: C, 27.25; H, 3.03; N, 7.95. Found C, 26.71; H, 2.95; N, 7.56.

***trans*-[PtCl(MeBzSO)(py)$_2$]NO$_3$** The same general conditions were used as for the previous complex but with two equivalents of sulfoxide ligand. Upon evaporation to an oil, acetone was added to dissolve the excess of MeBzSO and the product was precipitated out with ether. Upon cooling, the white solid was filtered off, recrystallized from MeOH/ether and washed with acetone to remove any remaining free ligand. The product was dried in vacuum with heat. Yield 45 % Anal. Calcd. for $C_{18}H_{20}ClN_3O_4SPt$: C, 35.73; H, 3.31; N, 6.95. Found C, 35.93; H, 3.11; N, 6.70.

***trans*-[PtCl(Me$_2$SO)(pic)$_2$]NO$_3$**. The same general reaction conditions were used as above. Yield 68 % Anal. Calcd. for $C_{14}H_{20}ClN_3O_4SPt$: C, 30.19; H, 3.59; N, 7.55. Found C, 30.51; H, 3.94; N, 7.53.

***trans*-[PtCl(MeBzSO)(pic)$_2$]NO$_3$**. The same general conditions were used as above but again with two equivalents of sulfoxide ligand. Upon evaporation to an oil the product was precipitated out with ether. After cooling overnight, the white solid was filtered off, recrystallized from hot MeOH/ether and washed with acetone to remove the excess of free ligand. The product was dried in vacuum with heat. Yield 53 % Anal. Calcd. for $C_{19}H_{22}ClN_3O_4SPt$: C, 37.94; H, 3.79; N, 6.64. Found C, 38.08; H, 3.73; N, 6.63.

Implementation of the claimed invention will generally involve identifying patients suffering from tumors and administering the platinum coordination compound in an acceptable form by an appropriate route. The dosage to be administered is usually determined in Phase I clinical trials and may vary depending on the age, gender, weight and overall health status of the individual patient, as well as the nature of the cancer itself.

Administration can be oral or parenteral, including intravenously, intramuscularly, subcutaneously, etc., or by other routes (e.g. transdermal, sublingual, aerosol, etc.).

The compounds can be administered in the pure form or in a pharmaceutically

acceptable formulation including suitable elixirs, binders, and the like or as pharmaceutically acceptable salts or other derivatives. It should be understood that the pharmaceutically acceptable formulations and salts include liquid and solid materials conventionally utilized to prepare injectable dosage forms and solid dosage forms such as tablets and capsules. Water may be used for the preparation of injectable compositions which may also include conventional buffers and agents to render the injectable composition isotonic. Other potential additives include: colorants; surfactants (TWEEN, oleic acid, etc.); and binders or encapsulants (lactose, liposomes, etc). Solid diluents and excipients include lactose, starch, conventional disintergrating agents, coatings and the like. Preservatives such as methyl paraben or benzalkium chloride may also be used. Depending on the formulation, it is expected that the active composition will consist of 1-99% of the composition and the vehicular "carrier" will constitute 1-99% of the composition. The pharmaceutical compositions of the present invention may include any suitable pharmaceutically acceptable additives or adjuncts to the extent that they do not hinder or interfere with the therapeutic effect desired of the Pt complex.

The administration of pharmaceutical compositions of the present invention can be intermittent, or at a gradual or continuous, constant or controlled rate to a patient. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Further, the effective dose can vary depending upon factors such as the mode of delivery, gender, age, and other conditions of the patient, as well as tumor type and stage or grade.

Generally, for parenteral administration in humans, dosages in the range of from about 0.1 to about 500 mg active Pt compound/kg body weight/24 hr., more preferably 1.0 to 10.0 active Pt compound/kg body weight/24 hr., are effective. The level of efficacy and optimal amount of dosage for any given Pt complex may vary from complex to complex.

In the following examples, objects and advantages of this invention are further illustrated by various embodiments thereof but the details of those examples should not be construed to unduly limit this invention.

EXAMPLES

Methods

The cytotoxicity of the novel *trans*-platinum compounds was assayed through the standard protocols of the NCI Developmental Therapeutics (HIV) and NIAID (Herpes Viruses) Screening Programs. See the following websites for details of the protocols:

http://dtp.nih.gov/docs/aids/aids_screen.html

http://www.niaid.nih.gov/dmid/apdsame.html.

IC_{50} is cytotoxic dose in cell carriers.

EXAMPLE 1. Cytotoxicity Studies with Platinum Nucleobase Compounds

The cytotoxicity of several nucleobase compounds of the general formula *SP*-4-2-$[PtX(L)(L')(B)]^+$ was assessed and the results are given in Table I. The cell lines employed were human foreskin fibroblast (HFF), Daudi, and CEM-SS, a T-cell line typically used to carry and maintain human immunodefficiency virus (HIV). The IC_{50} values for HFF and Daudi cell lines were determined by cell proliferation as referenced above. The IC_{50} values for the CEM-SS cell line was determined by XTT colorimetric assays as referenced above.

The following abbreviations apply to Table II: 4-pic, 4-picoline; tz, thiazole; bztz, benzothiazole; quin, quinoline; *i*quin, *iso*quinoline; 9-EtGua, 9-ethylguanine; 1-MeCyt, 1-methylcytosine.

TABLE I.

				IC_{50} (μM) for indicated cell line			
Compound	L	L'	B	HFF	Daudi	CEM-SS	CEM-SS
1	NH_3	NH_3	9-EtGua	18.9	7.9		
2	NH_3	tz	9-EtGua	11.2	18.1	47.3	24.6
3	NH_3	bztz	9-EtGua	11.2	9.8		
4	NH_3	quin	9-EtGua	25.9	0.93	47.4	31.7
5	NH_3	*i*quin	9-EtGua	2.8	4.8		
6	4-pic	4-pic	9-EtGua	21.7	0.92	1.9	2.0

7	NH_3	NH_3	1-MeCyt	>45.2	15.0		
8	NH_3	tz	1-MeCyt	>52.0			
9	NH_3	quin	1-MeCyt	38.7	14.1	50.4	33.2
10	NH_3	*i*quin	1-MeCyt	>56.4	21.6		

As can be seen, some exceptionally cytotoxic agents such as Compound 6 were produced. The cytotoxicity is equivalent to that of parent *trans*-$[PtCl_2(4\text{-pic})_2]$ but Compound 6 adds significant water-solubility and bioavailability over the parent compound. Such cytotoxic activity has previously correlated well with that of water-soluble platinum compounds such as cisplatin. Therefore, it is likely that these and other similar compounds of the general formula $[PtX(L)(L')(B)]^+$ will display anti-tumor activity *in vivo*.

EXAMPLE 2. Cytotoxicity Studies with Platinum Sulfoxide Compounds

The cytotoxic properties of the platinum complex *trans*-$[PtCl(Me_2SO)(pyridine)_2]^+$ were assessed both in vitro and in vivo. The results, which are depicted below in Table II, showed *in vitro* cytotoxicity equivalent to the parent *trans*-$[PtCl_2(pyridine)_2]$ in human ovarian A2780 cells. In initial *in vivo* studies in animals (murine L1210 leukemia), the dimethylsulfoxide complex exhibited some antitumor activity (T/C of > 150% is considered indicative of *in vivo* activity). In contrast, as previously found and reported (J. Med. Chem. 32:2240 (1989) the parent dichloride is totally inactive. Thus, the concept of water-solubilization to give equivalent cytoxicity and enhanced *in vivo* activity is confirmed.

TABLE II.

Complex	**A 2780[a]**	**L1210 Leukemia[b]**
	IC_{50}(μg/mL)	**%T/C (Dose, schedule)**
trans-$[PtCl(Me_2SO)(pyridine)_2]^+$	0.3	155 (50 x 3)
trans-$[PtCl_2(pyridine)_2]$	0.2	106 (50 x 2)

a: IC_{50} values calculated according to Farrell, N., Tam, T.B. Ha, Souchard, J.-P., Wimmer, F.L., Cros, S., and Johnson, N.P.: Cytostatic *trans*-Platinum(II) Complexes. J. Med. Chem. 32:2240 (1989) and Farrell, N., Qu, Y., and Hacker, M.P.: Cytotoxicity and Antitumor Activity of Bis(platinum) Complexes. A Novel Class of Platinum Complexes Active in Cell Lines Resistant to Both Cisplatin and 1,2-Diaminocyclohexane Complexes. J. Med. Chem. 33:2179 (1990).

b: %T/C is % average survival in days of treated animals/average survival in days of control animals. All tests performed as reported in references in a above. 50 x 3 refers to dose (mg/kg) and schedule (drug injection at 1,5,9 days after tumor inoculation). The parent dichloride was injected twice only because treated animals died at same rate of controls, again indicating no activity.

While the invention has been described in terms of its preferred embodiments, those skilled in the art will recognize that the invention can be practiced with modification within the spirit and scope of the appended claims. Accordingly, the present invention should not be limited to the embodiments as described above, but should further include all modifications and equivalents thereof within the spirit and scope of the description provided herein.

We claim:

1. A method for treating tumors in patients, comprising the step of administering to a patient in need thereof an effective amount of a platinum coordination compound of the general formula:

SP-4-2-[PtX(L)(L')(B)]$^+$

wherein,

X is an anionic ligand;

L and L' are selected from the group consisting of NH_3 and substituted or unsubstituted heterocyclic amines where the substituents are electrophilic or nucleophilic, and L and L' may be the same or different, and

B is a sulfoxide or a heterocyclic nucleobase with a nitrogen in a ring which is connected to Pt.

2. The method of claim 1 wherein said platinum coordination compound is *trans*-[PtCl(Me_2SO)(pyridine)$_2$]$^+$,

3. The method of claim 1 wherein said platinum coordination compound is *trans*-[PtCl(9-ethylguanine)(NH_3)$_2$]$^+$.

4. The method of claim 1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(thiazole)]$^+$.

5. The method of claim 1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(benzothiazole)]$^+$.

6. The method of claim 1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(quinoline)]$^+$.

7. The method of claim 1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(*iso*quinoline)]$^+$.

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8. The method of claim 1 wherein said platinum coordination compound is *trans*-[PtCl(9-ethylguanine)(4-picoline)$_2$]$^+$.

9. The method of claim 1 wherein said platinum coordination compound is *trans*-[PtCl(1-methylcytosine)(NH_3)$_2$]$^+$.

10. The method of claim1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(thiazole)]$^+$.

11. The method of claim 1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(quinoline)]$^+$.

12. The method of claim 1 wherein said platinum coordination compound is *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(*iso*quinoline)]$^+$.

13. The method of claim 1 wherein said step of administration is oral or parenteral.

14. A method of killing tumor cells, comprising the step of contacting said tumor cells with a platinum coordination compound of the general formula:

SP-4-2-[PtX(L)(L')(B)]$^+$

wherein,

X is an anionic ligand;

L and L' are selected from the group consisting of NH_3 and substituted or unsubstituted heterocyclic amines where the substituents are electrophilic or nucleophilic, and L and L' may be the same or different, and

B is a sulfoxide or a heterocyclic nucleobase with a nitrogen in a ring which is connected to Pt.

15. The method of claim 14 wherein said platinum coordination compound is *trans*-[PtCl(Me_2SO)(pyridine)$_2$]$^+$,

16. The method of claim 14 wherein said platinum coordination compound is *trans*-[PtCl(9-ethylguanine)$(NH_3)_2$]$^+$.

17. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(thiazole)]$^+$.

18. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(benzothiazole)]$^+$.

19. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(quinoline)]$^+$.

20. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(*iso*quinoline)]$^+$.

21. The method of claim 14 wherein said platinum coordination compound is *trans*-[PtCl(9-ethylguanine)(4-picoline)$_2$]$^+$.

22. The method of claim 14 wherein said platinum coordination compound is *trans*-[PtCl(1-methylcytosine)$(NH_3)_2$]$^+$.

23. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(thiazole)]$^+$.

24. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(quinoline)]$^+$.

25. The method of claim 14 wherein said platinum coordination compound is *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(*iso*quinoline)]$^+$.

26. The method of claim 14 wherein said step of administration is oral or parenteral.

27. A compound having the formula *trans*-[PtCl(Me_2SO)(pyridine)$_2$]$^+$.

28. A compound having the formula *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(thiazole)]$^+$.

29. A compound having the formula *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(benzothiazole)]$^+$.

30. A compound having the formula *SP*-4-2-[PtCl(9-ethylguanine)(NH_3)(*iso*quinoline)]$^+$.

31. A compound having the formula *trans*-[PtCl(9-ethylguanine)(4-picoline)$_2$]$^+$.

32. A compound having the formula *trans*-[PtCl(1-methylcytosine)(NH_3)$_2$]$^+$.

33. A compound having the formula *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(thiazole)]$^+$.

34. A compound having the formula *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(quinoline)]$^+$.

35. A compound having the formula *SP*-4-2-[PtCl(1-methylcytosine)(NH_3)(*iso*quinoline)]$^+$.

36. A method for enhancing the water solubility of a *trans*-platinum compound of the general formula *trans*-[PtX_2(L)(L')], where L and L' are NH_3 or a substituted or unsubstituted heterocyclic amine and X is an anionic ligand, comprising,

replacing one X substituent with a sulfoxide or a heterocyclic nucleobase.

37. The method of claim 36 wherein the *in vivo* activity of said *trans*-platinum compound is also enhanced.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/27387

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 33/24; C07F 15/00
US CL : 514/184, 185, 186, 187, 188, 492; 544/225; 546/2, 10; 548/101, 108; 556/137

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/184, 185, 186, 187, 188, 492; 544/225; 546/2, 10; 548/101, 108; 556/137

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN/CAS, strucure search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUNDQUIST et al. Solvolysis Reactions of cis- and trans-Diamminedichloroplatinum(II) in Dimethyl Sulfoxide. Structural Characterization and DNA Binding of trans-[Pt(NH3)2 (Me2SO)Cl]+. Inorgan. Chem. 1987, Vol. 26, No. 10, pages 1524-1528, whole document.	36, 37

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Richard L. Raymond

Telephone No. (703) 308-1235

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